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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
PARAS JR, PETER	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 03/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/721,997	HAUSER ET AL.	
	Examiner	Art Unit	
	Peter Paras, Jr.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-35* is/are pending in the application.

4a) Of the above claim(s) *30-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 April 2004* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11262003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 11-35 are pending.

Election/Restrictions

Applicant's election with traverse of Group I, claims 11-29, in the reply filed on 1/10/06 is acknowledged. The traversal is on the ground(s) that searching all the claims would not present an undue search burden. This is not found persuasive because it is maintained that each of the inventions is distinct from the other and would require a separate search that is not coextensive. For example, the cDNA of Group I could be used to produce a protein or as a probe in a hybridization assay *in vitro*, while the proteins of Group II could be used to produce an antibody in an animal, the method of Group III is used to treat a disease by gene therapy, and the method of Group IV is used to treat a disease by protein therapy. Therefore, it is maintained the inventions are distinct each from the other, having separate uses.

The requirement is still deemed proper and is therefore made FINAL.

Claims 30-35 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 1/10/06.

Specification

The disclosure is objected to because of the following informalities: the instant application is not in compliance with the sequence rules (see below).

Appropriate correction is required. Failure to comply with the sequence rules will be considered non-responsive

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) as follows: figure 1 contains unidentified sequences.

Applicant must provide the following to be in compliance with the sequence rules: 1) an initial or substitute computer readable form (CRF) copy of the sequence listing; 2) an initial or substitute paper copy of the sequence listing, as well as an amendment directing its entry into the specification; 3) a statement that the content of the paper and computer readable copies are the same and, where applicable include no new matter, as required by 37 CFR 1.821 (e), 1.821 (f), 1.821 (g), 1.825 (b) or 1.825 (d); and 4) an amendment to the specification to include an appropriate sequence identifier that properly identifies each sequence in the specification.

Abstract

Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:
Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c).

Priority

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Claim Objections

Claims 11-29 are objected to because of the following informalities: claims 11 and 20 should begin with the article "A". Appropriate correction is required. Claims 12-19 and 29 depend from claim 11. Claims 21-29 depend from claim 20.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 11-29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to modified human factor VIII cDNA, recombinant host cells and vectors comprising the same modified human factor VIII cDNA, and a method of producing the same modified human factor VIII cDNA.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1117. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1116.

The sequences of all modified human factor VIII cDNAs that encode modified factor VIII polypeptides having a half-life of greater than three minutes encompassed within the genus of modified human factor VIII cDNAs have not been disclosed. Based

upon the prior art there is expected to be sequence variation among the species of modified human factor VIII cDNA sequences. The specification has asserted that modified human factor VIII polypeptides (encoded by the modified factor VIII cDNA sequences) having a half-life of greater than 3 minutes would be useful in treating hemophilia. The specification contemplates that various mutations including those shown in Figures 2-3 would result in a factor VIII having a half-life of greater than 3 minutes. The specification however has not disclosed the sequences of any of the modified human factor VIII cDNAs encoding factor VIII mutants having a half-life of greater than 3 minutes. There is no evidence on the record of a relationship between the structures of the embraced modified human factor VIII cDNA molecules that would provide any reliable information about the structure of cDNA molecules within the genus. There is no evidence on the record that embraced modified human factor VIII cDNA molecules had known structural relationships to each other; the art indicated that there is variation between sequences of various modified human factor VIII cDNA molecules. The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which is not conventional in the art as of applicants effective filing date. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998).

In the instant case, the claimed embodiments of modified human factor VIII cDNA molecules that encode modified factor VIII polypeptides having a half-life of greater than 3 minutes encompassed within the genus of modified factor VIII cDNA molecules lack a written description. The specification fails to describe what DNA molecules fall into this genus. The skilled artisan cannot envision the detailed chemical structure of the encompassed regulatory elements, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

In view of the above considerations, one of skill in the art would not recognize that applicant was in possession of the necessary common features or attributes possessed by member of the genus of modified human factor VIII molecules encoding modified factor VIII polypeptide having a half-life of greater than 3 minutes. Moreover, the art has recognized that there would be variation among the species of the genus of modified human factor VIII cDNA sequences. Therefore, Applicant was not in possession of the genus of modified human factor VIII cDNAs that encode modified

factor VIII polypeptides having a half-life of greater than 3 minutes as encompassed by the claims. University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that to fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention."

Claims 18-19 and 27-28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated recombinant host cell, does not reasonably provide enablement for any recombinant host cells in vivo. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims embrace recombinant host cells comprising a modified factor VIII cDNA.

The specification contemplated introduction of the embraced modified factor VIII cDNA into a patient for the purpose of treating hemophilia. Clearly, such a contemplation falls into the realm of gene therapy. See the specification at page 10 as well as throughout the entire document. The specification has failed to provide any guidance for introducing a modified factor VIII cDNA into a patient that would correlate to a therapeutic effect, particularly when the modified factor VIII cDNA encodes a modified factor VIII polypeptide having a half-life of greater than 3 minutes. Moreover, the specification has failed to provide guidance with respect to vector, route of

administration, or level of expression that would correlate to expression of a modified factor VIII *in vivo* for the purpose of treating hemophilia. Since the instant specification has failed to provide specific guidance or working examples correlating to a recombinant host cell in vivo comprising a modified factor VIII cDNA, one of skill in the art could not rely on the state of the gene therapy art to produce a recombinant host cell in vivo comprising a modified factor VIII cDNA; there appears to be no other purpose, provided by the specification, for a recombinant host cell *in vivo* than to provide therapy. This is because the art of gene therapy is an unpredictable art with respect cell targeting, levels of expression of a therapeutic protein necessary to provide therapy, and mode of administration of the therapeutic gene. These issues are discussed by two published reviews. Verma *et al.* teach that as of 1997, "there is still no single outcome that we can point to as a success story" (page 239, col. 1). The authors go on to state, "Thus far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression" (page 239, col. 3). Anderson (1998) states that "there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of a human disease" (page 25, col 1) and concludes, "Several major deficiencies still exist including poor delivery system, both viral and no-viral, and poor gene expression after genes are delivered" (page 30). Besides the general expectation that it will require years of further research to develop effective gene therapy (Anderson, page 30), it would require extensive research to understand the fundamental biology of the system. With regard to expression of factor VIII in a recombinant cell, Soukharev et al (Blood Cells, Molecules, and Diseases, 2002, 28(2): 234-248) observed that factor VIII is

expressed at different levels in various cell types *in vitro*. See page 236, at column 1. The specification however, has failed to provide guidance as to which cell type would be optimal for expressing and secreting modified factor VIII *in vivo*, the route of administration for targeting the desired cell type or the type of vector necessary to introduce a modified factor VIII cDNA into the desired cell type and achieve a sufficient level of expression for treatment of hemophilia. Given the lack of guidance provided by the specification it would have required undue experimentation to make and use the invention as claimed without a reasonable expectation of success.

Therefore, in view of the quantity of experimentation necessary to determine the parameters listed above for a recombinant host cell *in vivo* comprising a modified factor VIII, the lack of direction or guidance provided by the specification correlating to a recombinant host cell *in vivo* comprising a modified factor VIII, the absence of working examples for the demonstration or correlation to a recombinant host cell *in vivo* comprising a modified factor VIII, the unpredictable state of the art with respect to expression levels of modified factor VIII *in vivo*, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

Claims 14-15 and 23-24 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. 37 CFR 1.118 (a) states that "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application".

Claims 14-15 are directed to a modified human factor VII cDNA comprising at least one transcriptional regulatory element, which is a dominant selectable marker.

Claims 23-24 are directed to a modified human factor VIII cDNA comprising at least one transcriptional regulatory element, which is a dominant selectable marker.

With respect to claims 14-15, the specification as originally filed provided no implicit or explicit support for a modified human factor VII. The specification has only provided support for modified human factor VIII.

With respect to claims 23-24, the specification as originally filed provided no implicit or explicit support for a modified human factor VIII comprising at least one transcriptional regulatory element, which is a dominant selectable marker. The specification has contemplated transcriptional regulatory elements as being part of an expression vector for expressing factor VIII. See page 7. The specification as originally filed provided no implicit or explicit support for a transcriptional regulatory element that is a dominant selectable marker. The specification has contemplated dominant selectable markers as encoded by genes that are separate from factor VIII and transcriptional regulatory elements. See page 8.

Applicants are reminded that it is their burden to show where the specification supports any amendments to the claims. See 37 CFR 1.121 (b)(2)(iii), the MPEP 714.02, 3rd paragraph, last sentence and also the MPEP 2163.07, last sentence.

MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02

teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application. MPEP 2163.06 further notes "When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. *Applicant should therefore specifically point out the support for any amendments made to the disclosure.*

Claim Rejections - 35 USC § 112, 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 11-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 11 embraces modified human factor VIII cDNA comprising at least one replaced codon, wherein the replaced codon corresponds to an amino acid of porcine factor VIII. The claim is indefinite as written because it is not understood how a first codon of a human factor VIII cDNA corresponds to an amino acid of porcine factor VIII. What is the amino acid of porcine factor VIII, which corresponds to a first codon of a

human factor VIII? It is not understood how a human factor VIII codon corresponds to a porcine factor VIII codon. The specification has failed to define such a correspondence. The sequences of human and porcine factor VIII are of different lengths. Therefore, it is not understood how the sequences correspond to each other. Appropriate correction is required. Claims 12-19 and 29 depend from claim 11.

Claim 20 embraces modified human factor VIII cDNA comprising at least one replaced codon, wherein the replaced codon corresponds to an amino acid of mutant human factor VIII. The claim is indefinite as written because it is not understood how a first codon of a human factor VIII cDNA corresponds to an amino acid of a mutant human factor VIII. What is the amino acid of mutated human factor VIII, which corresponds to a first codon of a human factor VIII? It is not understood how a human factor VIII codon corresponds to a mutated human factor VIII codon. The specification has failed to define such a correspondence. The sequences of a mutated human and factor VIII has not been provided. Therefore, it is not understood how the sequences correspond to each other. Appropriate correction is required. Claims 21-29 depend from claim 20.

Claims 13 and 22 recite the limitation "the deleted B-domain or segment thereof" in lines 1-2. There is insufficient antecedent basis for this limitation (the deleted B-domain segment) in the claim.

Claims 14-15 recite the limitation "the modified human factor VII cDNA" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claims 14 and 23 are directed to a cDNA comprising a transcriptional regulatory element. The claim is indefinite as written because cDNAs are not known to comprise transcriptional regulatory elements. A cDNA is in operable linkage with a transcriptional regulatory element since a transcriptional regulatory element directs expression of the cDNA. A transcriptional regulatory element does not comprise any coding sequences, as does a cDNA. Therefore, it is not understood how a cDNA can comprise a transcriptional regulatory element. Appropriate correction is required.

Claims 15 and 24 are embrace a transcriptional regulatory element that is a dominant selectable marker. The claim is indefinite as written because a transcriptional regulatory element is not known to be a dominant selectable marker. A dominant selectable marker is a protein encoded by a gene. A transcriptional regulatory element does not comprise any coding sequences, as does a cDNA. Therefore, it is not understood how a transcriptional regulatory element can be a dominant selectable marker. Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 11-19 are rejected under 35 U.S.C. 102(b) as being anticipated by Negrier et al (US 6,271,025).

The claims are directed to modified human factor VIII cDNAs, vectors comprising the same, and host cells comprising the same vectors and cDNAs.

Negrier et al taught modified human factor VIII cDNA that comprises a deleted B-domain, wherein the B-domain was replaced with four arginines, which are interpreted to read be encoded by a linker segment. See columns 1-2. Also, Negrier et al taught replacement of codons near the Kozak consensus sequence (column 2, lines 27-38). Since there correlation between human factor VIII and either porcine or mutated human factor VIII is not clear as discussed in the section under 35 USC 112, 2nd paragraph, the human factor VIII cDNA sequences of Negrier et al anticipated the modified human factor VIII cDNA sequences embraced by the claims. The B-domain deleted factor VIII cDNA was introduced into an expression vector that comprised a transcriptional regulatory element and a gene encoding a dominant selectable marker. The expression vector was then transfected into CHO cells (the transfection reaction mix of expression vector and cells is interpreted to read on a modified factor VIII cDNA and a pharmaceutically acceptable carrier), which were selected by resistance to G418; the resistance to G418 is provided by a dominant selectable marker encoded by a gene contained within the expression vector. See columns 3-4. The transfected CHO cells expressed and produced modified factor VIII. See columns 4-6. The modified factor VIII was identified on a Western blot by an antibody.

Thus, the teachings of Negrier et al anticipated all of the instant claim limitations.

Claims 11, 19, 20, 28 and 29 are rejected under 35 U.S.C. 102(b) as being anticipated by Pipe et al (Biochemistry, 1997, 94: 11851-11856; IDS).

The claims are directed to modified human factor VIII cDNAs, vectors comprising the same, host cells comprising the same cDNAs, and a method of producing a modified human factor VIII cDNA.

Pipe et al taught a modified human factor VIII cDNA. Since there correlation between human factor VIII and either porcine or mutated human factor VIII is not clear as discussed in the section under 35 USC 112, 2nd paragraph, the human factor VIII cDNA sequences of Pipe et al anticipated the modified human factor VIII cDNA sequences embraced by the claims. Pipe et al further taught transfection of COS-1 cells with the modified factor VIII cDNA and subsequent purification of the modified human factor VIII by immunoaffinity chromatography. See pages 11851-11852.

Thus, the teachings of Pipe et al anticipated all of the instant claim limitations.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter Paras, Jr. whose telephone number is 571-272-4517. The examiner can normally be reached on M-Th, 7-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Inquiries of a general nature or relating to the status of the application should be directed to Dianiece Jacobs whose telephone number is (571) 272-0532.

Peter Paras, Jr.

Art Unit 1632

PETER PARAS, JR.
PRIMARY EXAMINER